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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
12/20/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/573,821	OKUNO ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *49,51-56,59-62,67 and 68* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *49, 51-56, 59-62, 67, and 68* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of October 7, 2011, in response to the action mailed July 7, 2011, is acknowledged. It is acknowledged that Claims 1-48, 50, 57, 58, 63-66 are cancelled and Claims 49, 51, 55, and 56 have been amended. Claims 49, 51-56, 59-62, 67, and 68 are pending and are hereby considered.

Interview Summary

Regarding the Interview Summary in Applicants' current remarks (p9) it is stated:

> "Examiners admitted that (1) Applicants' amendments would overcome at least some rejections, e.g., the rejection under 35 U.S.C. §§ 101 and 102; and (2) the cancellation of claims 36-48, 50, 57-58, and 63-66 would render some aspects of the other rejections mooted, as acknowledged with the withdrawal of the rejections."

No such admission was made by the Office. See the Interview summary mailed July 14, 2011 stating: "No agreement was reached." As explained in the Advisory Action of February 16, 2011: "Amendment of Claim 49 and 51 requires additional search and consideration."

Special Status

Applicants state that "On and after March 28, 2011, the application … will have a 'special' status under M.P.E.P. § 707.02 and should be processed accordingly." It is acknowledged that the instant Application was filed on March 28, 2006 and, thus, has "special" status under M.P.E.P. § 707.02. Therefore, the application has been carefully studied by the supervisory patent examiner.

Priority

The English translation of JP 2003-342183, filed October 7, 2011, is acknowledged. Claims 49, 51-56, 59-62, and 67 are accorded the benefit of JP 2003-342183, filed September 20,

2003. However, it is noted that JP 2003-342183, filed September 20, 2003, does not disclose the complete subject matter of Claim 68.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Rejection of Claim 62 under U.S.C. 112, first paragraph/written description, for reasons set forth in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The claimed processes are directed to [using] a variant of the E. coli OmpT protease (parent) having the amino acid sequence of SEQ ID NO: 41, wherein the Asp97 is replaced with the recited amino acid (D97L, D97H, or D97M).

(A) Reply: It is acknowledged that the Claim 49 has been so amended.

(B) Additionally, the claims recite cleaving a polypeptide with an E. coli OmpT protease variant having the recited amino acid sequence, wherein the polypeptide comprises a cleavage site (P1↓P1'), and wherein the variants and the cleavage sites are arranged according to the table below:

	The 97[th] Amino Acid of the Variant	Cleavage Site	
		P1	P1'
I	Leucine (D97L)	Arginine or Lysine	Serine or Alanine
II	Methionine (D97M)	Arginine or Lysine	Phenylalanine, Alanine, Serine, Cysteine, or Tyrosine
III	Histidine (D97H)	Arginine or Lysine	Alanine, Valine, Isoleucine, Methionine, Serine, Threonine, Cysteine, or Asparagine

The claims are directed to "cleaving" polypeptides having the recited motifs. Giving the claims their broadest reasonable interpretation consistent with the specification, the claim reads on cleaving with any degree of efficiency. See, e.g., In re Morris, 127 F.3d 1048, 1054, 44 U.S.P.Q.2d 1023, 1027 (Fed. Cir. 1997). Amino acid residues outside the P1↓P1' may at best affect the cleavage efficiency. Applicants submit that the present claims do not recite cleavage efficiency. Accordingly, the alleged unpredictability is irrelevant in determining whether the present claims comply with the written description requirement.

(B) Reply: It is acknowledged that the claims do not recite cleavage efficiency.

Claim 62 encompasses using the D97L, D97H, and D97M variants of SEQ ID NO: 41 to cleave any polypeptide having at the P7 to P1 positions ^{7}DARRRAR^{1}↓ (SEQ ID NO: 12), i.e., having an acidic Asp at position P7. It is acknowledged that the specification discloses that the D97M variant can cleave the peptide MHAAAAAADARRRAR↓FVPIFTYG ELQRMQEKERNKGQ having SEQ ID NO: 12 at positions P7 to P1 (Fig 15&18). However, the specification fails to provide any evidence that either the D97L or D97H variant of SEQ ID NO: 41 cleaves at any motif comprising SEQ ID NO: 12 at positions P7 to P1. Moreover, the specification teaches that (i) the parent protease of SEQ ID NO: 41 does not cleave, at all, the peptide MHGYDAELRLYR↓FVPIFTYGELORMOEKERNKGO (Fig5-6) having an acidic Asp

at position eight and (ii) that situating an Asp up-stream of the cleavage site, including P7, inhibits cleavage by the parent protease (Example 8). Based on the fact that the specification clearly teaches that an Asp up-stream of the cleavage site blocks the ability of a substrate to be cleaved, the skilled artisan would believe that, more likely than not, Applicants were not in possession of a method for cleaving any peptide comprising ^{7}DARRRAR$^{1}\downarrow$ (SEQ ID NO: 12) using the D97L or D97H variant of SEQ ID NO: 41.

(C) Furthermore, the Office's assertion as to inadequacy of working examples ("functional permutations") is unsupported. Working examples covering the full scope of the claims are not required for an adequate written description.

(C) Reply: It is acknowledged that examples covering the full scope of the claims are not required for an adequate written description. But, see (B), above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 49 and 51-53 under 35 U.S.C. 103(a) as being unpatentable over the combination of Okuno et al, 2002a, Dekker et al, 2001, and Kramer et al, 2001 in view of Metzler, 2001, as described in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The Office exaggerates Kramer's teachings as to the role of Asp97 in the P1' specificity of OmpT protease. Kramer does not teach that Asp97 of the OmpT protease determines its P1' specificity. Applicants direct the Office to lines 2 to 8, left col., at page 429 of Kramer:

> "Assuming that the substrate has an extended conformation and that the P 1 site chain points toward Glu27 and Asp208, the P1' chain would be located close to Asp97. D97A OmpT displayed only 6% residual activity, therefore we propose that Asp97 is responsible for the observed P1' specificity."

The skilled artisan would have understood that Kramer merely speculates as to the role of Asp97 in the P1' specificity. Thus, there can be no reasonable expectation that the replacement of Asp97 with other amino acid(s) would have changed substrate specificity, let alone the presently claimed amino acid substitutions (D97L, D97H, and D97M) of Asp97.

(A) Reply: It is acknowledged that Kramer et al so states. The Office's position is that said statement would motivate the skilled artisan to make and test the OmpT variants having the alternative 18 amino acid residues at position 97. As a minimum, motivation derives from (e) "obvious to try" of KSR. See the action of July 7, 2011 (p10-11) for a further discussion of KSR as pertains to the instant rejection.

(B) Given the knowledge in the field at the time (Olsen et al, 2000), there was no motivation to make and use the claimed E. coli OmpT protease variants. An objective of Olsen is to produce OmpT variants with enhanced cleavage at Arg↓Val (p1072 ¶4). To achieve this objective, Olsen generated a library of OmpT variants by random mutagenesis, and assayed for variants with increased activity against various substrates (p1074). Screening identified three OmpT variants having enhanced cleavage rates for Arg↓Val (Table 1). Each variant contains

multiple substitutions (Table 2). However, none of the substitutions is at the 97th amino acid residue (Asp97) of OmpT protease.

(B) Reply: Applicants appear to assert that Olsen et al teaches away from making and testing the alternative 18 OmpT protease variants having substitutions at position 97. This is not persuasive for the following reasons.

(1) Since the claims recite only the D97M OmpT variant as cleaving at Arg↓Val, only this variant is relevant to the instant argument.

(2) There is no evidence that Olsen et al screened the D97M OmpT variant or any variant comprising a D97M substitution. The skilled artisan would know that the number of variants encompassed by a percent identity does not increase in a linear manner with a decrease in identity. This non-linear increase in the number of variants is due to the fact that each residue of the parent protein can be altered independently and each altered residue can be substituted with any one of the alternative 19 amino acids. The OmpT of SEQ ID NO: 41 consists of 297 amino acids. Patrick et al, 2003 teaches (p451 ¶2):

> "Even a small protein of 100 amino acids can be encoded by 4^{300} » 10^{181} possible DNA sequences, a number vastly larger than the number of atoms in the observable Universe (~10^{80}), let alone the biggest protein-encoding libraries accessible in the laboratory [10^{12}-10^{15} using in vitro selection methods such as mRNA display".

Thus, the probability of the D97M OmpT variant or any variant comprising a D97M substitution being comprised within the library of Olsen et al is extremely low.

(3) Olsen et al teaches that there is little homology among the amino acid changes in the three variants identified (p1073 ¶5). Thus, residues other than D97 have an effect on substrate specificity of OmpT protease. Nonetheless, the fact that residues other than D97 have an effect

on substrate specificity of OmpT protease does not provide prima facie evidence that D97 does not affect P1' substrate specificity, as proposed by Kramer et al.

Thus, the Office fails to agree that Olsen et al teaches away from making the alternative 18 OmpT protease variants having substitutions at position 97 and testing said variants using the substrates of Okuno et al, 2002a and Dekker et al, 2001.

(C) The Office also fails to explain why a skilled artisan at the time would have been motivated to achieve the claimed combinations between the claimed E. coli OmpT protease variants and the claimed cleavage sites. The claims recite inter alia cleaving a polypeptide with an E. coli OmpT protease variant having the recited amino acid substitution (D97L, D97H, or D97M), wherein the combinations between the claimed 97th amino acid substitution of the E. coli OmpT protease variant and the claimed cleavage site (P1↓P1') are further elucidated below:

	The 97[R] Amino Acid of the Variant	Cleavage Site	
		P1	P1'
1	Leucine (D97L)	Arginine	Serine
2		Arginine	Alanine
3		Lysine	Serine
4		Lysine	Alanine
5	Methionine (D97M)	Arginine	Phenylalanine
6		Arginine	Alanine
7		Arginine	Serine
8		Arginine	Cysteine
9		Arginine	Tyrosine
10		Lysine	Phenylalanine
11		Lysine	Alanine
12		Lysine	Serine,
13		Lysine	Cysteine
14		Lysine	Tyrosine
15	Histidine (D97H)	Arginine	Alanine
16		Arginine	Valine
17		Arginine	Isoleucine
18		Arginine	Methionine
19		Arginine	Serine
20		Arginine	Threonine
21		Arginine	Cysteine
22		Arginine	Asparagine
23		Lysine	Alanine
24		Lysine	Valine
25		Lysine	Isoleucine
26		Lysine	Methionine
27		Lysine	Serine
28		Lysine	Threonine
29		Lysine	Cysteine
30		Lysine	Asparagine

Accordingly, the claimed methods only encompass altogether the above-enumerated thirty (30) combinations. The claimed combination set is only a small fraction (less than 1/250 or 0.4%) of the total possible combinations. Even if it were assumed arguendo that a skilled artisan were motivated to test the cleavage by a E. coli OmpT variant having an amino acid substitution at the 97th position (which it is not), there is no evidence on the record or adduced by the Office that a skilled artisan would have reached the presently claimed set of the combinations among all possible combinations.

(C) Reply: As explained in the prior action:

"…it would have been obvious to a person of ordinary skill in the art to make the OmpT protease AAA24430.1 variants having a substitution at Asp^{97} with each of the naturally occurring amino acids,

> including **Leu** and **Met,** and use said variants to cleave the fusion proteins of Okuno et al, 2002a (Tables 1&2) and the peptides of Dekker et al (Table 2), including those having a P1' of Ala or Phe. It is noted that the fusion proteins of Okuno et al, 2002a have the basic residue Arg at P4 (Tables 1&2). Motivation to do so is provided by the desire to examine the cleavage motif requirements of said variants by using the sequences of Okuno et al, and Dekker et al. The expectation of success is high, as the skilled artisan would have believed that, more likely than not the OmpT protease variants having a substitution at Asp^{97} with **Leu** or **Met** would cleave a substrate comprising a P1' that is S, A, F, C, Y, or V." (p9)

To reject a claim it is only necessary to reject a single species of the claim. The instant rejection is not based on the references rendering obvious cleaving the specific sub-set of the ~30 recited combinations. As explained in the prior actions, the instant rejection is based on testing the ability of the 18 OmpT variants to cleave the putative substrates of Okuno et al and Dekker et al. As also explained in the prior action: "Both Okuno et al, 2002a and Dekker et al teach genera of substrates having every one of the 20 naturally occurring amino acids at position P1'" (¶brdg p10-11). Thus, the combination of Okuno et al, Dekker et al, and Kramer et al, and Metzler would render obvious at least one species encompassed by each of Claims 49 and 51-53.

For these reasons and those explained in the prior actions, rejection of Claims 49 and 51-53 under 35 U.S.C. 103(a) as being unpatentable over the combination of Okuno et al, 2002a, Dekker et al, 2001, and Kramer et al, 2001 in view of Metzler, 2001, is maintained.

Rejection of Claims 49 and 51-53 under 35 U.S.C. 103(a) as being unpatentable over the combination of Okuno et al, 2002a, Dekker et al, 2001, and Kramer et al, 2001 in view of Wolf et al, 1995, as explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the same arguments presented above. These arguments are not found to be persuasive for the reasons following each argument above.

Rejection of Claims 54-56 59-61, 67, and 68 under 35 U.S.C. 103(a) as being unpatentable over the combination of Stumpe et al, 1998, Suzuki et al, 1972, and Kramer et al,

2001 in view of Yamamoto et al, 1996 and Metzler, 2001, as explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the same arguments presented above. These arguments are not found to be persuasive for the reasons following each argument above.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHERIDAN SWOPE whose telephone number is 571-272-0943. The examiner can normally be reached on 11a-7:30p7 EST.

If attempts to reach the examiner by telephone are unsuccessful after two business days, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652